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Ferrara, Italy

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

L' inflammasoma: la CPU (Central Processing Unit) della risposta infiammatoria

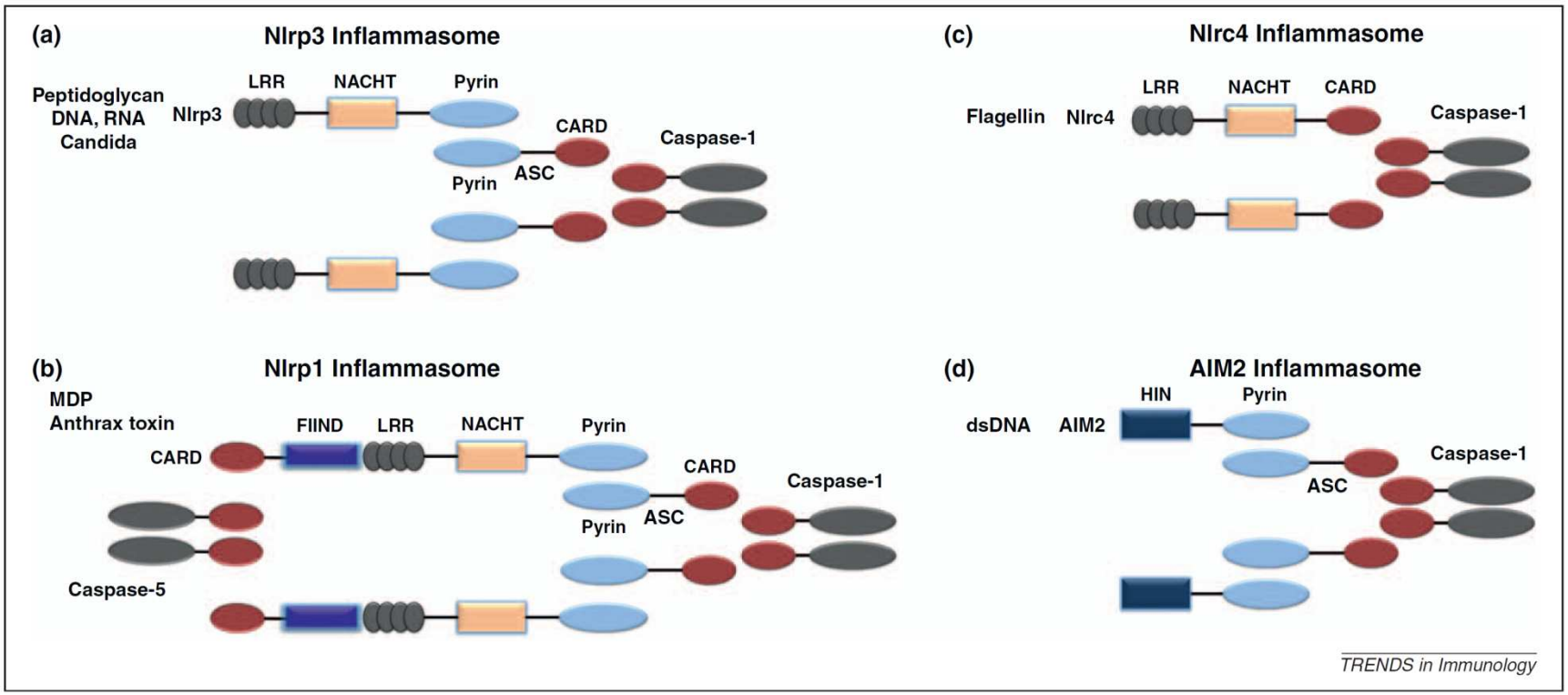
F. Di Virgilio

Ferrara, Maggio 2012

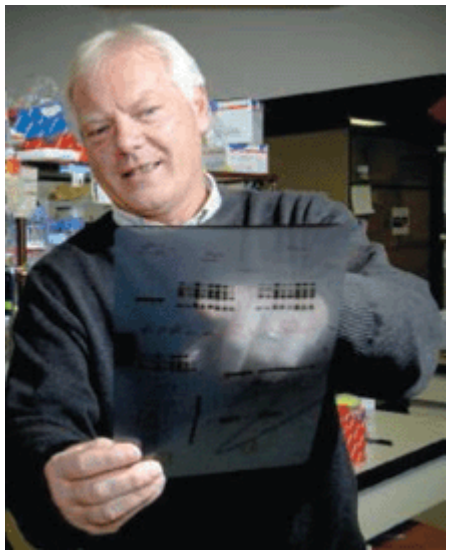
Sommario

1. Che cos’ è l’ inflammasoma
2. A che serve?
3. Conclusioni

Inflammasome subtypes



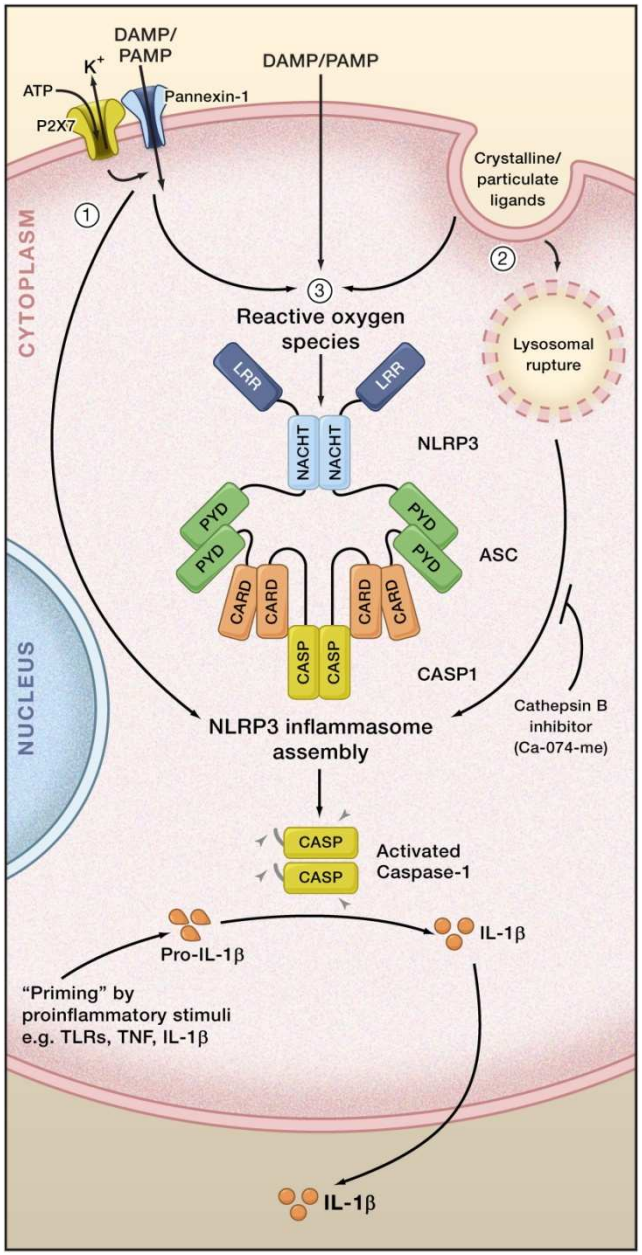
From van de Veerdonk et al, 2011



Jurg Tschopp
1951-2011
Dept. of Biochemistry
University of Lausanne

First reported about the “Inflammasome”
at a Conference in Maui in 2001

How a danger signal translates into activation of inflammation



From Schroeder and Tschopp, Cell 2010

Ludwig Institute for Cancer Research
Epalinges, Lausanne

October 22, 1988

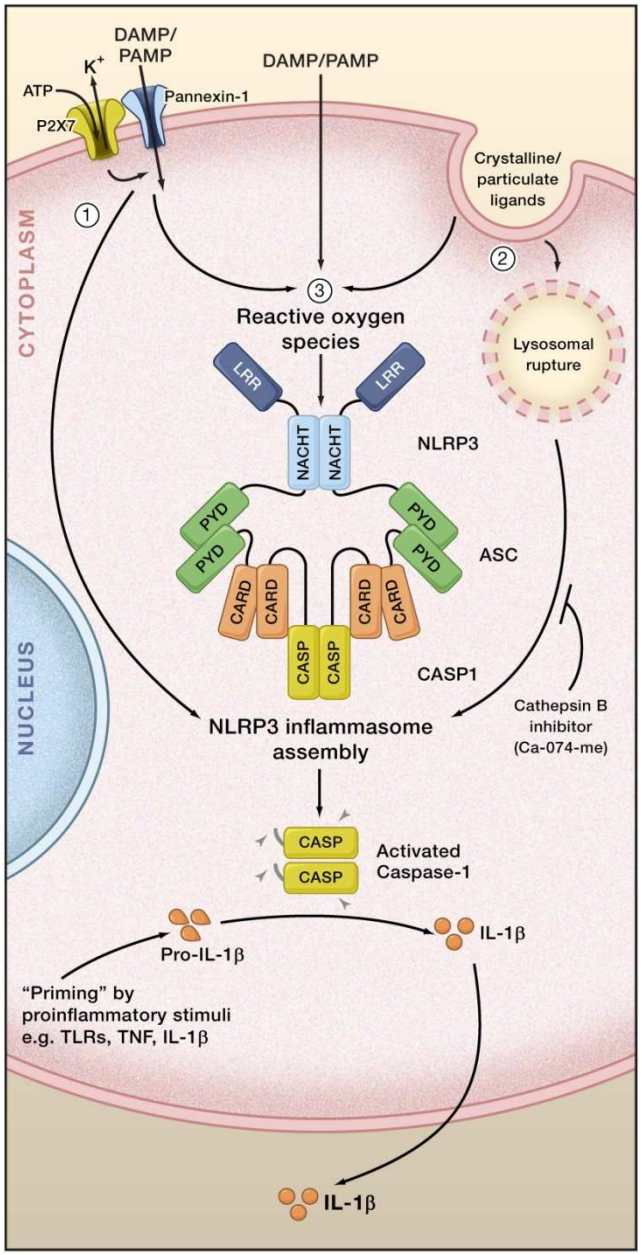
Seminars of the Department of Immunology

“The P2Z receptor of mouse macrophages”

Francesco Di Virgilio

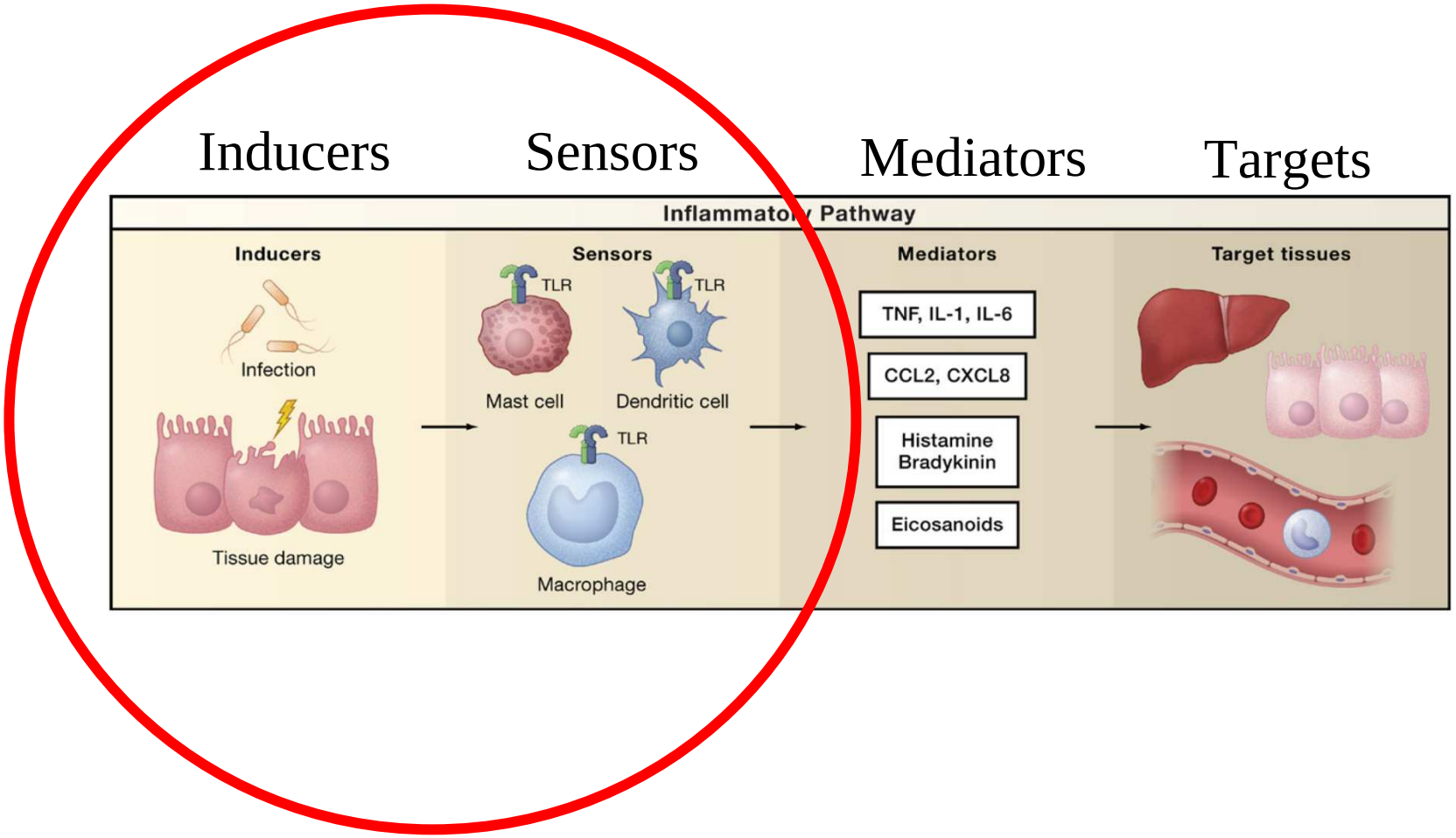
Host: Giampietro Corradin

How a danger signal translates into activation of inflammation



From Schroeder and Tschopp, Cell 2010

Basics of Inflammation



Inducers/Triggers

Viruses, bacteria, protozoa…….
Poisons, toxic, xenobiotics….
Cancer…..
Misfolded proteins
Cell and Tissue stressors…(ischemia!!!)
Metabolic dysfunction
Trauma
……..

Septic inflammation

Sterile inflammation

Sensors

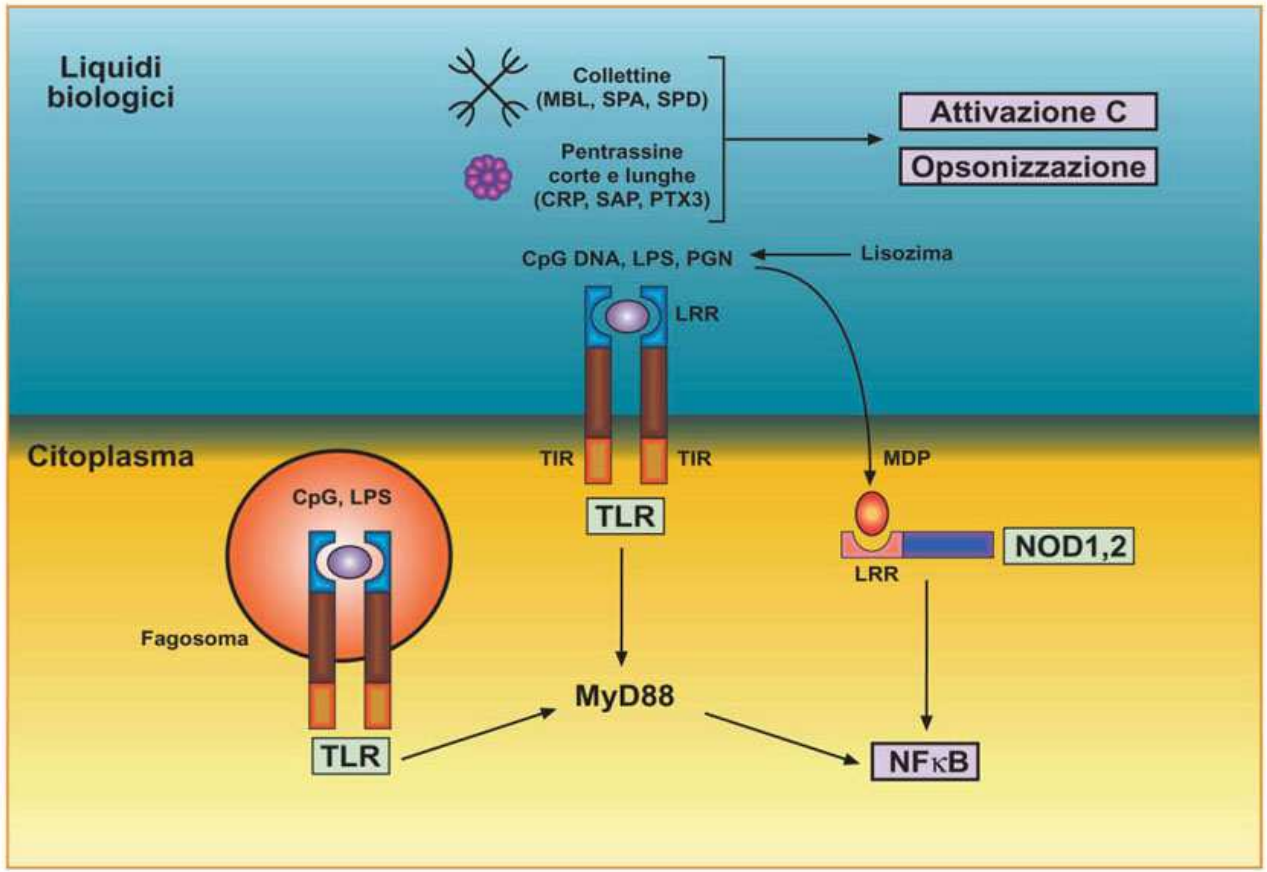
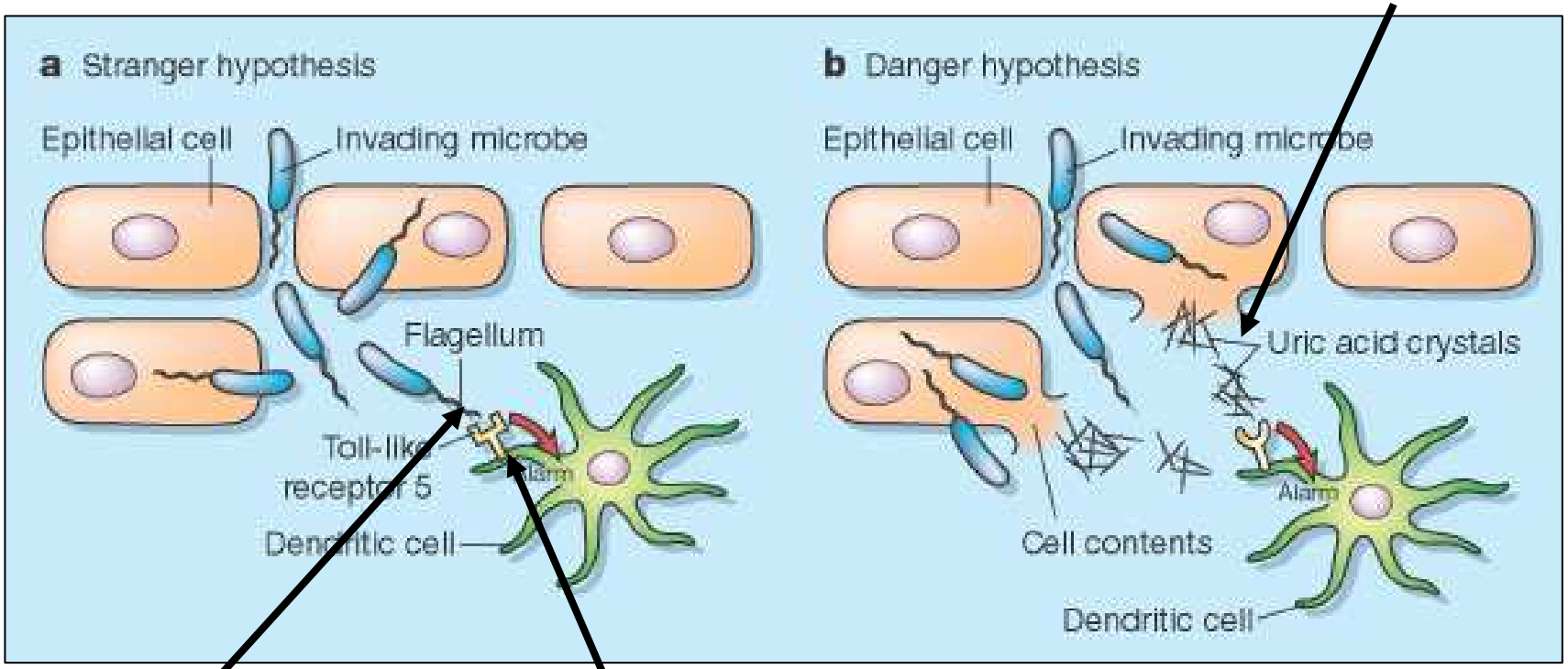


Figura 13.3 - I recettori dell'immunità innata e dell'infiammazione.
I recettori dell'immunità innata e dell'infiammazione riconoscono la presenza di patogeni o di tessuti danneggiati in compartimenti diversi: nei liquidi biologici, come recettori solubili (ante-antibodies); come recettori presenti sulla membrana plasmatica, come alcuni membri della famiglia dei Toll like receptors (es. TLR4 che riconosce la endotossina dei batteri Gram⁻); come recettori presenti sul fagolisosoma (es. TLR9 che riconosce sequenze ipometilate, CpG, tipiche del DNA batterico); come sensori citoplasmatici quali 2 proteine della famiglia NOD.

Dal volume: Pontieri "Patologia Generale" **Piccin Nuova Libraria S.p.A.**

How is inflammation started?

Stranger versus Danger



DAMP

PAMP

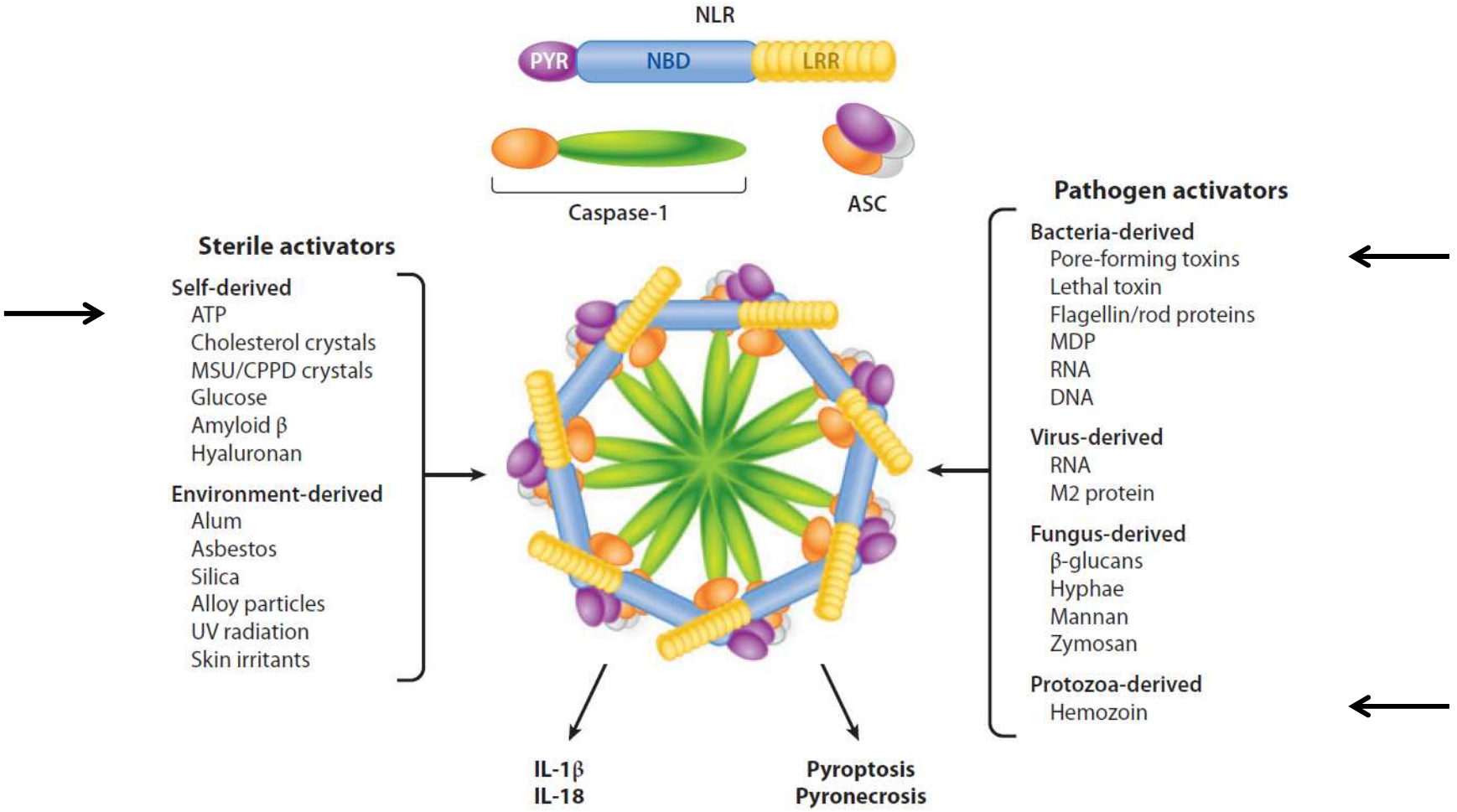
PRR

II - Sensing the damage

I - Sensing the pathogen

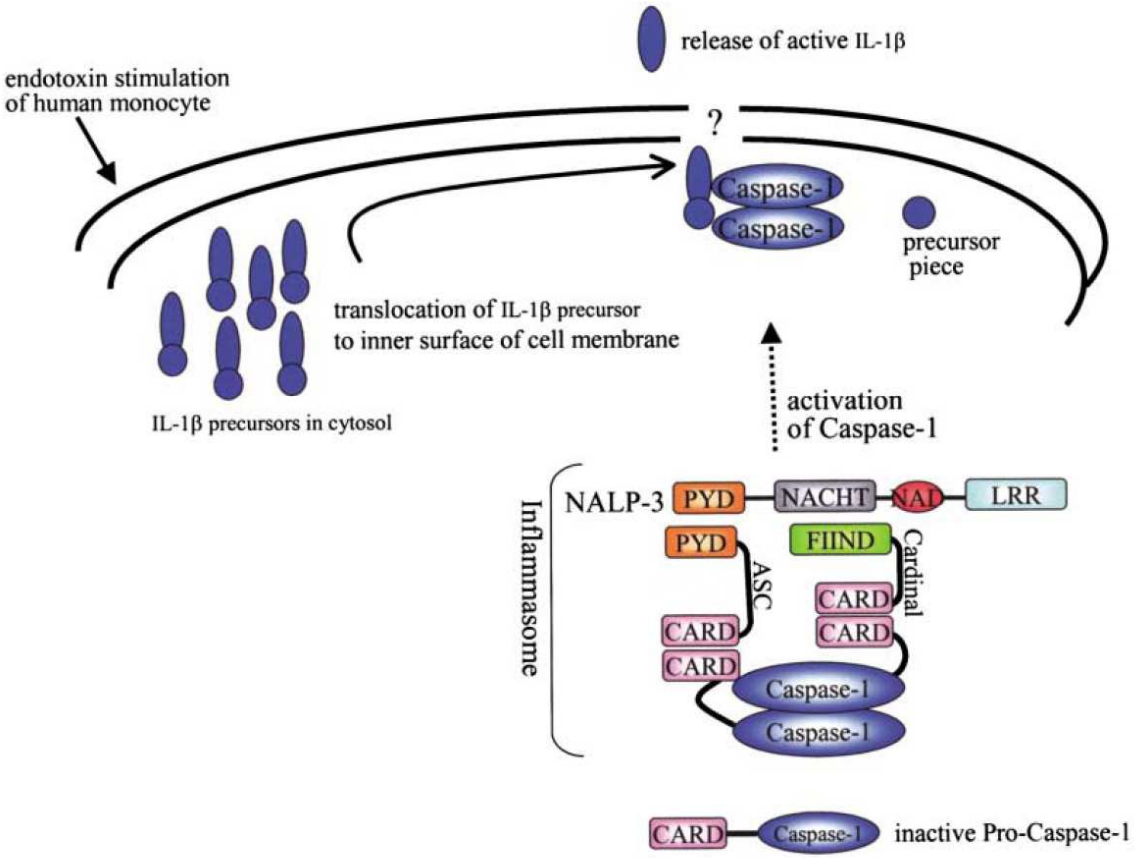
Modified from From Heath and Carbone, Nature 425:460-461, 2003

Inflammasome activators

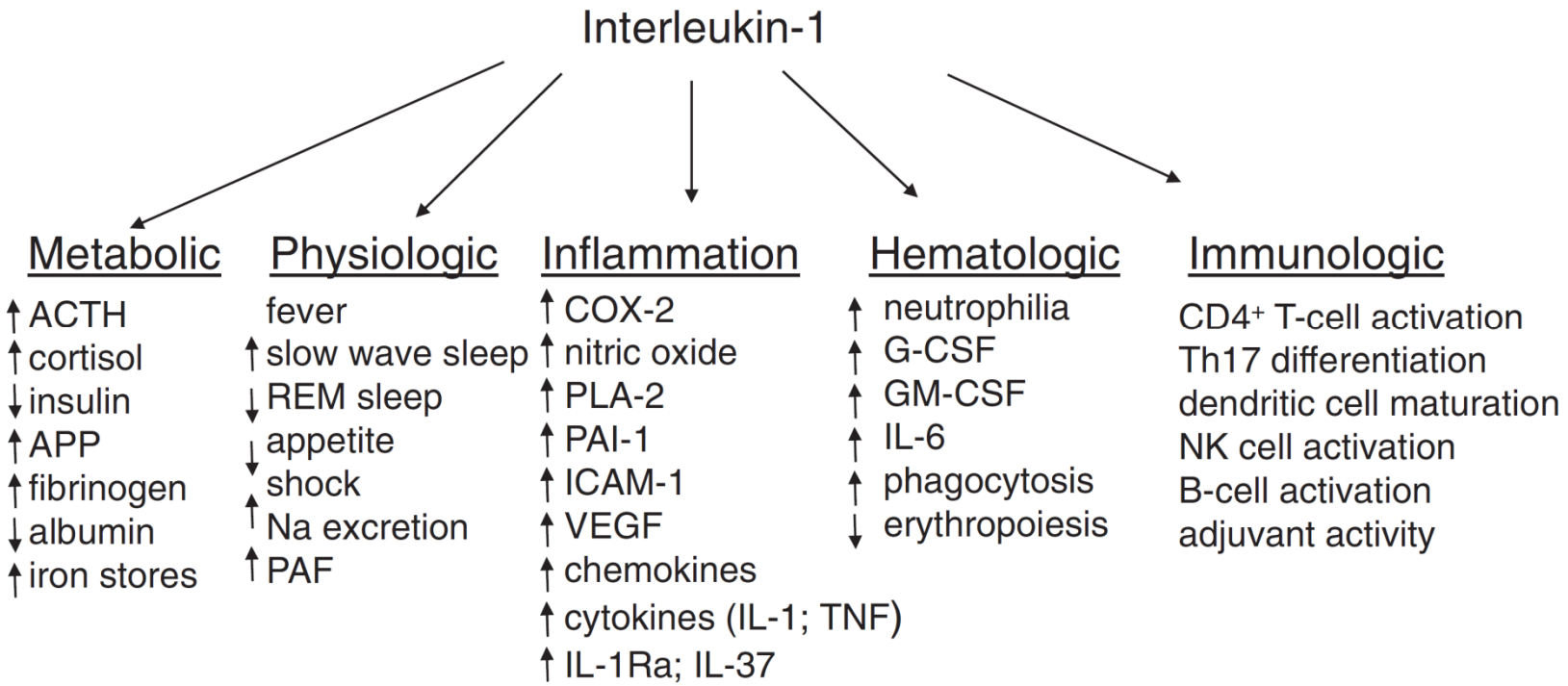


Modified from Davis et al, 2011

The Inflammasome: a IL-1β producing machinery



From Dinarello, 2005

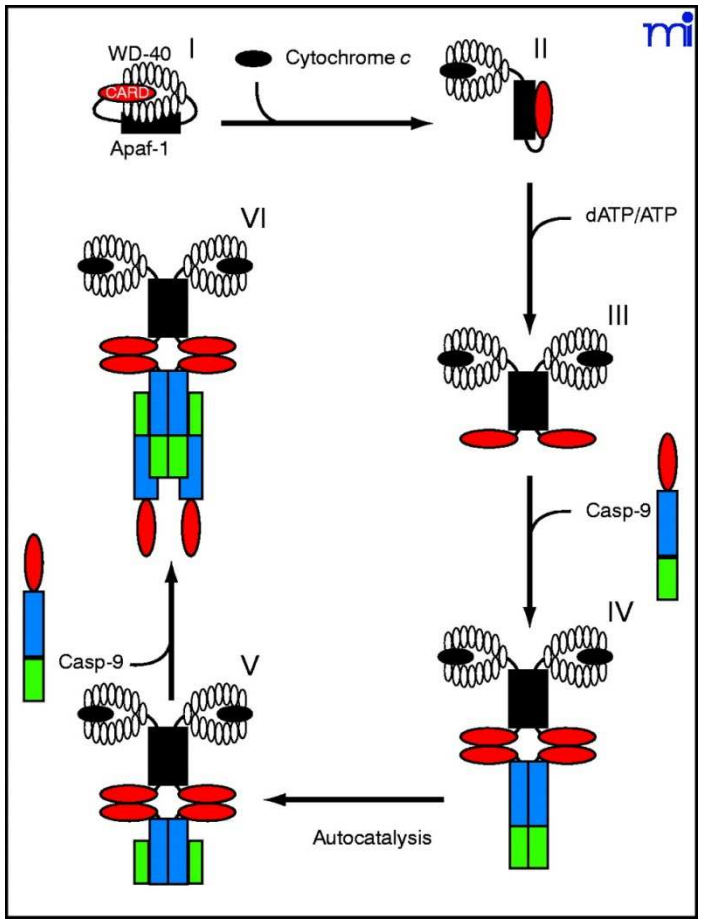


Dinarello 2011

Why “inflammasome?

Caspases are well known for their involvement in apoptosis

Initiator caspases are activated by “recruitment platforms” such as the Death-Inducing Signalling Complex (DISC) for caspase-8 or the apoptosome for caspase-9



Apoptotic proteases-activating factor: APAF

APAF-like proteins:

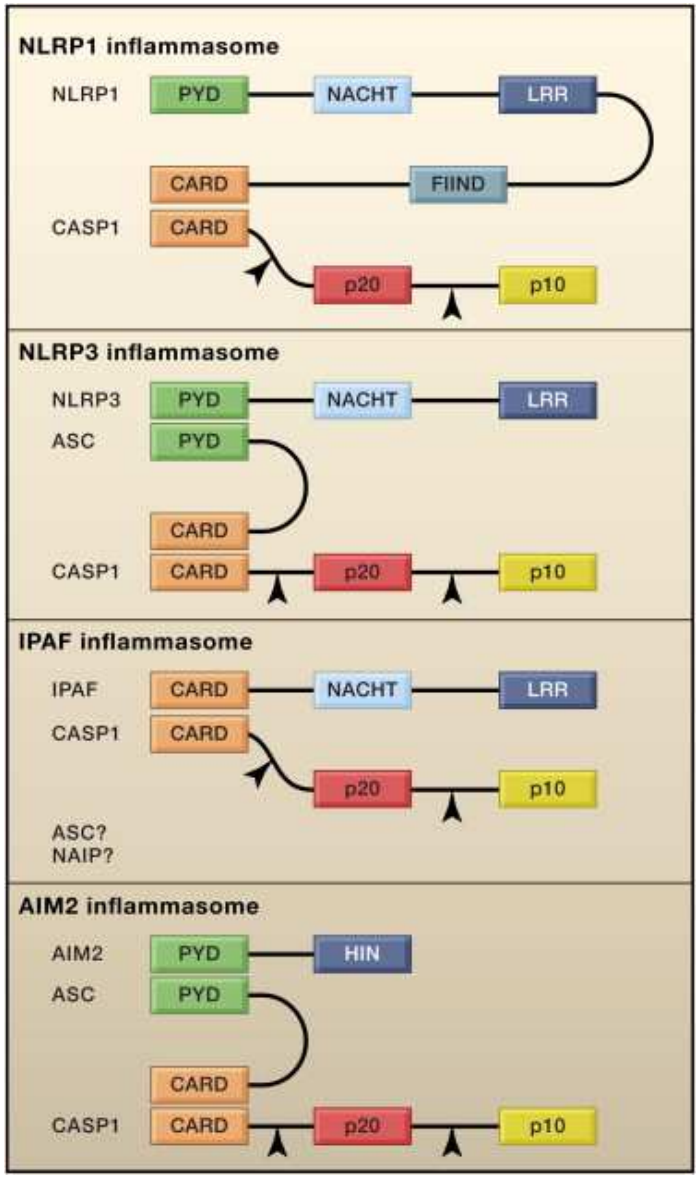
The NOD-Like Receptors (NLR)
NOD1, NOD2, NLRPs, IPAF, NAIPs

The apoptosome

From Hill et al., 2003, Mol Interv 3:19-26

“trigger”

The inflammasomes



From Schroeder and Tschopp, Cell 2010

Nucleotide-oligomerization domain

NLR: NOD-like receptors

NOD1
NOD2
NLRC3
NLRC5
NLRX1

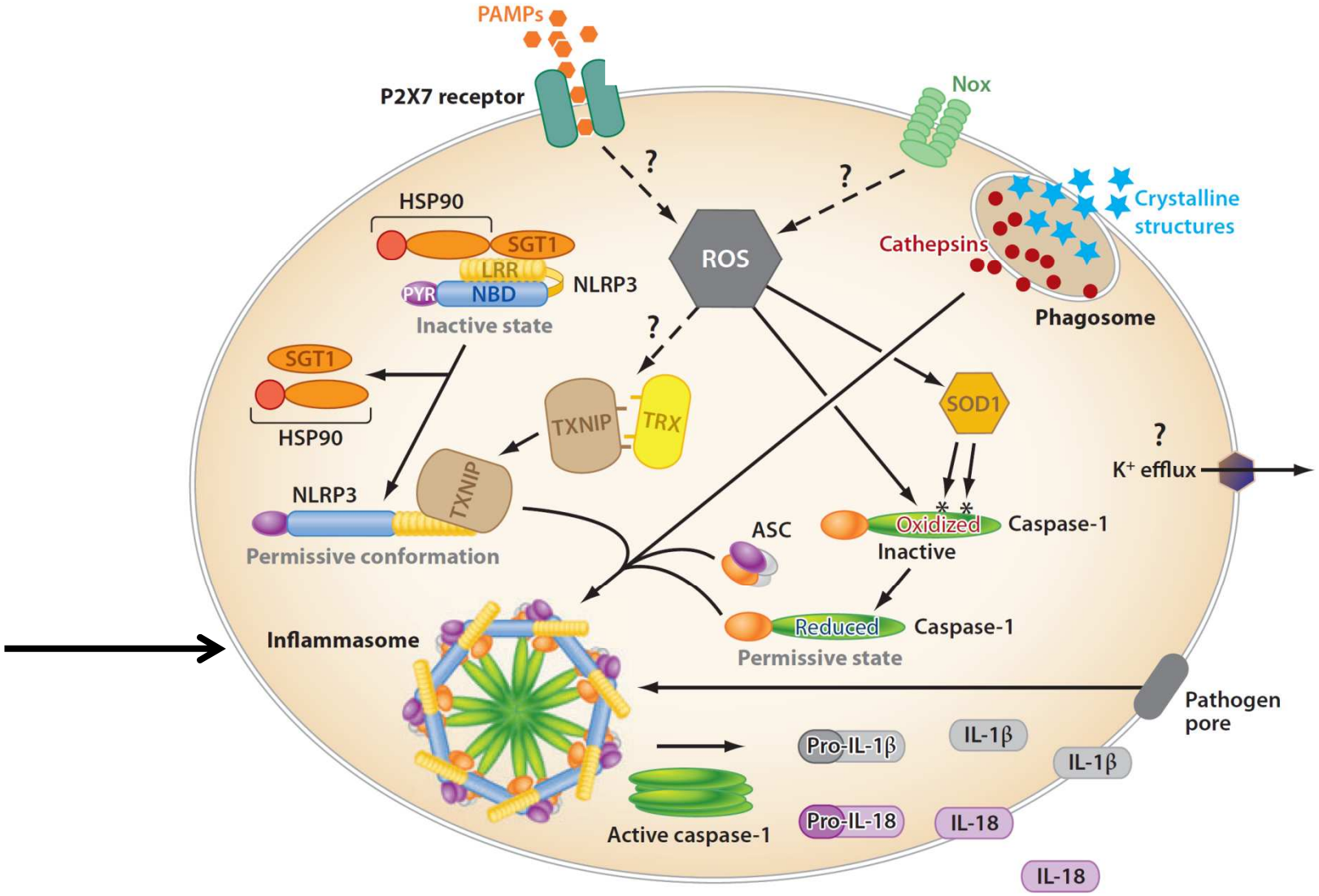
NALPs (NLRPs)

IPAF (NLRC4)

NAIP

CIITA

The inflammasome

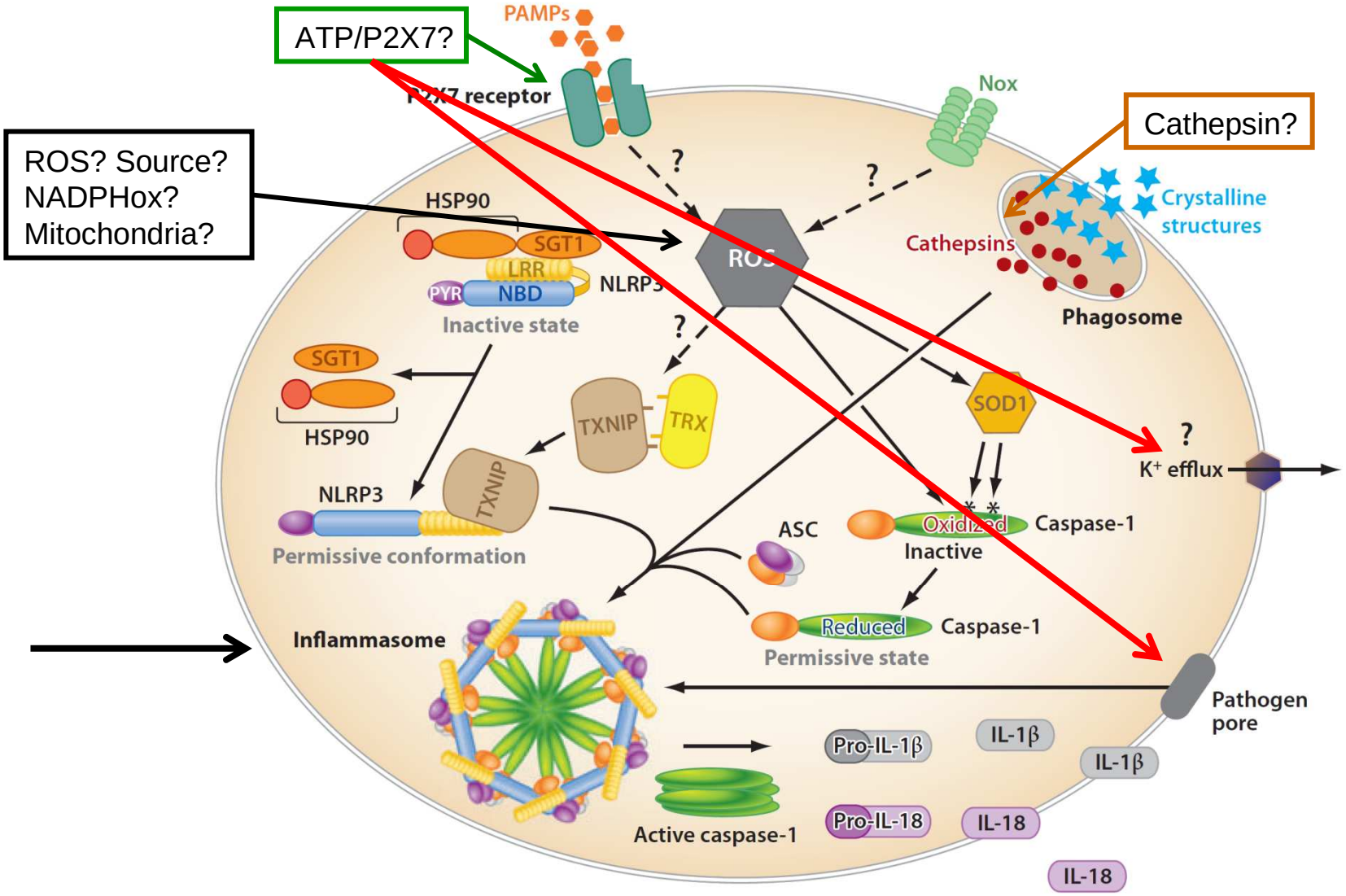


Modified from Davis et al, 2011

No evidence of direct ligand binding to the inflammasome

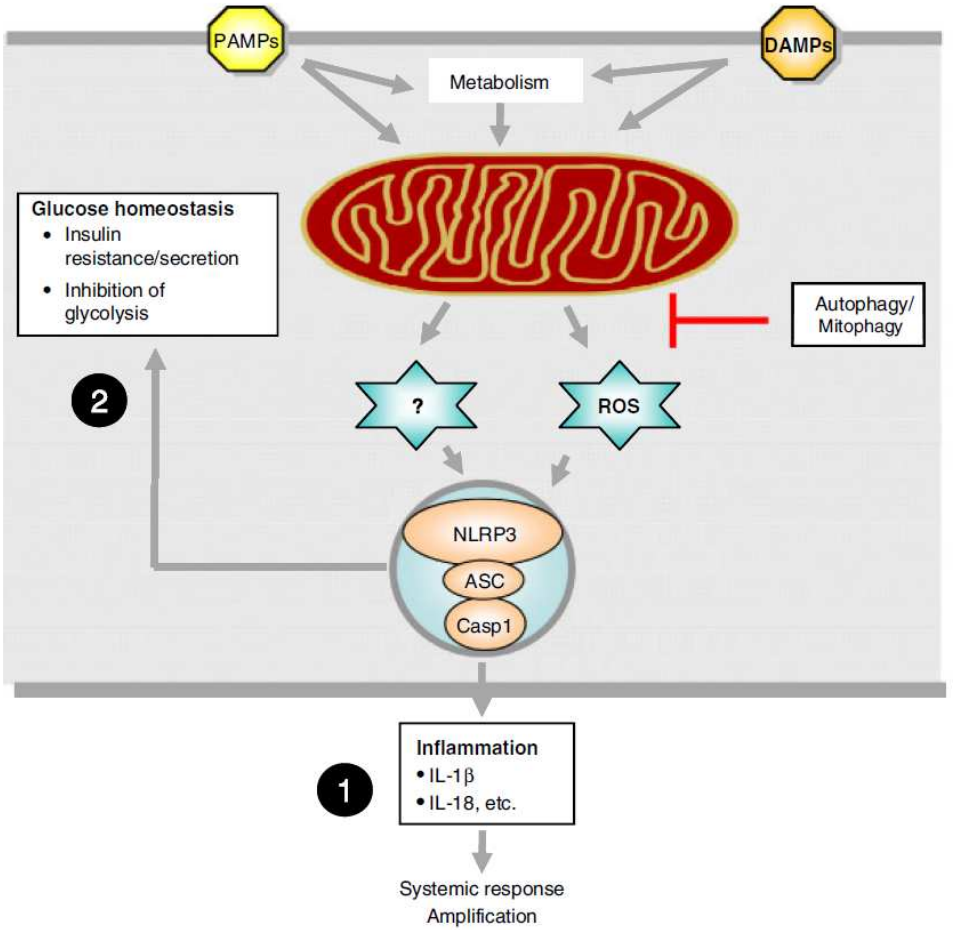
Might NLRP3 sense changes in the cellular milieu?

Models of activation of the inflammasome



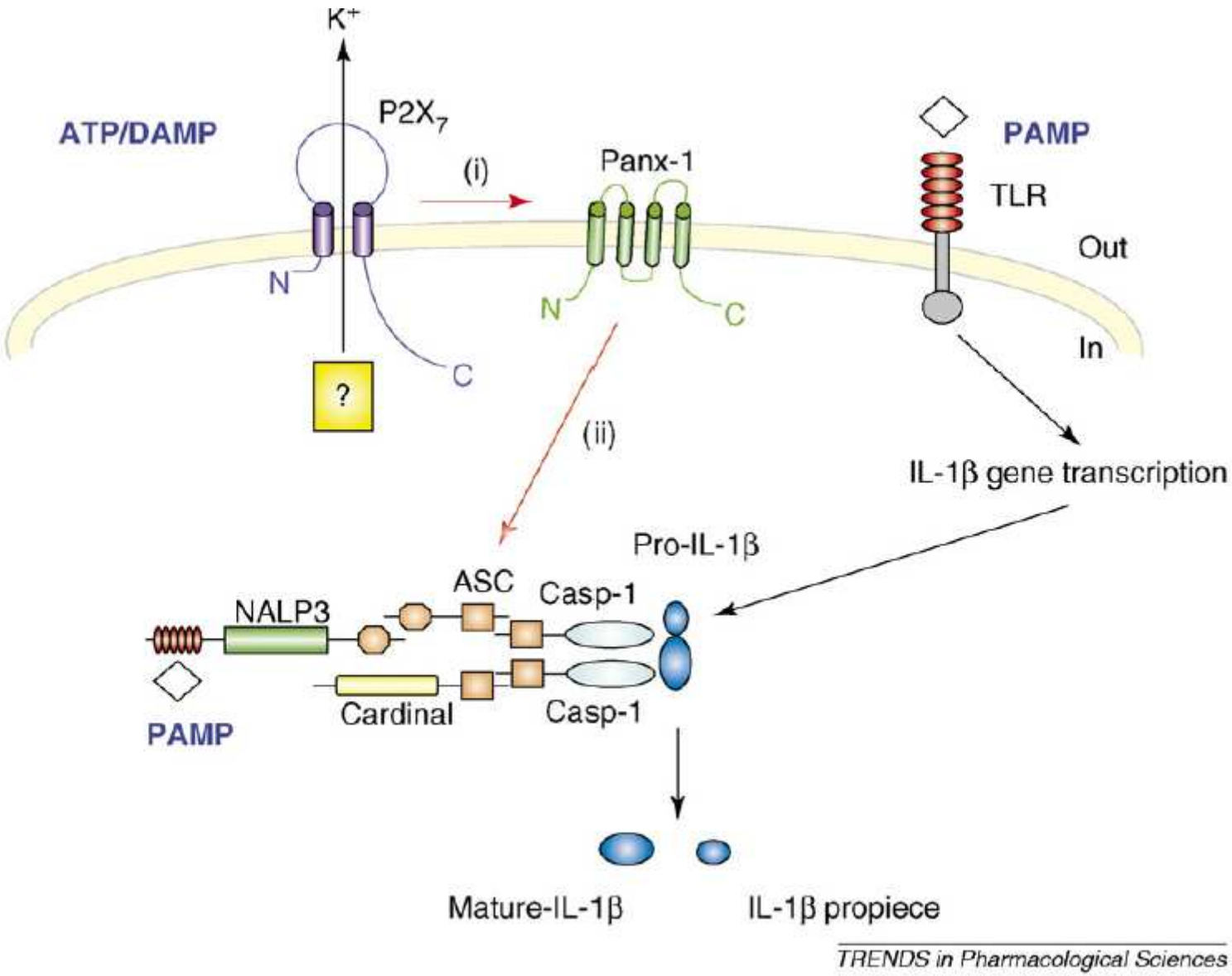
Modified from Davis et al, 2011

Mitochondria and inflammation



From Tschopp, 2011

The P2X7-inflammasome axis



Di Virgilio, TIPS 2007

Le inflammasomopatie

Disease	Gene (chromosome)	Protein (synonyms) or *pathogenic stimulus*
Type 1: IL-1β activation disorders (inflammasomopathies)		
Intrinsic		
FCAS[a], MWS[b], NOMID[c]/CINCA[d]	*NLRP3/CIAS1* (1q44)	NLRP3[e] (cryopyrin, NALP3, PYPAF1)
Extrinsic		
FMF[f]	*MEFV* (16p13.3)	Pyrin (marenostrin)
PAPA[g]	*PSTPIP1* (15q24–25.1)	PSTPIP1[h] (CD2BP1[i])
CRMO[j]/SAPHO[k]	Complex	
Majeed syndrome	*LPIN2* (18p11.31)	Lipin-2
HIDS[l]	*MVK* (12q24)	Mevalonate kinase
Recurrent hydatidiform mole	*NLRP7* (19q13)	NLRP7 (NALP7, PYPAF3, NOD12)
DIRA[m]	*IL1RN*	IL-1Ra
Complex/acquired		
Gout, pseudogout	Complex	*Uric acid/CPPD*
Fibrosing disorders	Complex	*Asbestos/silica*
Type 2 diabetes mellitus	Complex	*Hyperglycemia*
Schnitzler syndrome	Sporadic	

Conclusioni

L’ inflammasoma è un complesso proteico a localizzazione citoplasmatica responsabile dell’ attivazione della caspasi-1, e della conseguente conversione della pro-IL-1β in IL-1β.

Il meccanismo di attivazione non è ancora ben conosciuto, però è chiaro che l’ inflammasoma risponde alla presenza di PAMPS e DAMPS nell’ ambiente extracellulare e nel citoplasma.

Difetti nell’ attivazione/disattivazione dell’ inflammasoma sono alla base di numerose malattie infiammatorie croniche caratterizzate da ipersecrezione (locale o sistemica) di IL-1β.

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